JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 2004, **82,** 275–292 NUMBER 3 (NOVEMBER)

EFFECTS OF ANORECTIC DRUGS ON FOOD INTAKE UNDER PROGRESSIVE-RATIO AND FREE-ACCESS CONDITIONS IN RATS

MARK G. LESAGE, DAVID STAFFORD, AND JOHN R. GLOWA

LOUISIANA STATE UNIVERSITY HEALTH SCIENCES CENTER IN SHREVEPORT

The effects of two anorectic drugs, dexfenfluramine and phentermine, on food intake under different food-access conditions were examined. Experiment 1 compared the effects of these drugs on food intake under a progressive-ratio (PR) schedule and free-access conditions. Dexfenfluramine decreased food intake under both conditions, but the doses required to decrease intake under free-access conditions were higher than those required to reduce intake under the PR condition. Intermediate doses of phentermine sometimes increased breaking points, and higher doses decreased them. Phentermine decreased food intake at the same doses under both access conditions. Thus the potency of dexfenfluramine, but not phentermine, to decrease food-maintained behavior depended upon the food-access condition. Experiment 2 used a novel mixed progressive-ratio schedule of food delivery to study the duration of drug effects. Sessions consisted of five components separated by 3-hr timeouts. The ratio requirement reset at the beginning of each component and a new breaking point was obtained. Both dexfenfluramine and phentermine dose-dependently decreased breaking points early in the session. In some rats, compensatory increases in breaking point were observed. That is, breaking points later in the session increased over control levels, resulting in no change in the total number of food pellets earned for the session compared to control. The present findings suggest that the effects of some anorectic drugs depend upon the access conditions for food; increasing the effort to obtain food may enhance their ability to decrease food-maintained behavior.

Key words: progressive-ratio schedule, food-maintained behavior, food intake, dexfenfluramine, phentermine, lever press, rats

Pharmacotherapy involving the use of anorectic drugs (i.e., appetite suppressants) is commonly employed in the treatment of obesity (Bays & Dujovne, 2002; Spanswick & Lee, 2003). Preclinical research on the pharmacological modification of food-motivated behavior typically examines drug effects on the consumption of freely available food. This approach is based on the assumption that drugs decrease food consumption by decreasing the reinforcing efficacy of food (i.e., by producing satiety-like effects; Gibbs & Smith, 1982; Halford, Wanninayake, & Blundell, 1998). However, decreases in food intake under free-access conditions may also occur through other behavioral mechanisms, including an increase in the frequency of behaviors that are incompatible with feeding, motor impairment, or illness. None of these latter mechanisms would be a desirable outcome for clinical purposes. Thus it is important to examine food intake under a range of conditions in order to characterize more fully the behavioral mechanisms through which anorectics decrease food-maintained behavior.

Progressive-ratio (PR) schedules provide an alternative procedure for studying drug effects on food-motivated behavior (Hodos, 1961). These schedules require an increasing number of responses to produce successive reinforcers within a session. For example, a typical PR 5 schedule requires five responses to produce the first reinforcer, and the response requirement is incremented by five each time a reinforcer is earned. The breaking point, defined as either the largest ratio completed or the number of reinforcers earned in a session, is the primary dependent measure. Performance under PR schedules of food delivery is thought to reflect the efficacy or motivational strength of food, because increases in either deprivation level or

The authors would like to thank Katherine Dayton and Matt Feltenstein for their technical assistance during the course of this experiment. The authors also thank Wyeth-Ayerst Laboratories for supplying the dexfenfluramine. Procedures were conducted in accordance with the guidelines of the Animal Care and Use Committee of LSU Health Sciences Center in Shreveport. NIDA grants DA-09619, DA-05884-01, and DA-05877-01 supported this research. Mark LeSage is now at the Department of Medicine, Minneapolis Medical Research Foundation, Minneapolis, Minnesota. David Stafford is now at the Department of Psychology, Centenary College, Shreveport, Louisiana. John Glowa is now at CNS Discovery, Pfizer Global Research & Development, Groton, Connecticut.

Address correspondence to Mark G. LeSage, Department of Medicine, Minneapolis Medical Research Foundation, 914 South 8th Street, D3-860, Minneapolis, Minnesota 55404 (e-mail: mlesage@mmrf.org).

reinforcer magnitude typically increase breaking points (Hodos & Kalman, 1963; Kennedy & Baldwin, 1972).

Although food intake under PR schedules and free-access conditions both provide measures of the reinforcing efficacy of food, drugs can have different effects on these measures. For example, Jewett, Cleary, Levine, Schaal, and Thompson (1995) directly compared the effects of neuropeptide Y, insulin, and 2-deoxyglucose on food intake under a PR schedule and free-access conditions. Although all three drugs significantly increased food intake under free-access conditions, only neuropeptide Y significantly increased breaking points under the PR condition. These findings illustrate how a thorough characterization of drug effects on food-motivated behavior requires more than simply measuring the amount of food consumed under free-access conditions. Drug effects may be modulated by behavioral parameters (e.g., effort) that are not manipulated in the free-access paradigm, but are in other paradigms. To our knowledge, no similar studies have been reported that directly compare the effects of anorectic drugs on food intake under PR schedules and free-access conditions.

EXPERIMENT 1

The purpose of this experiment was to directly compare the effects of two anorectic drugs, dexfenfluramine (DEX) and phentermine (PHEN) on food intake under a PR schedule and free-access conditions, as measured by breaking points and grams consumed, respectively. Both drugs are phenethylamines that reduce food consumption under free-access conditions (e.g., Foltin, 1989; Garattini, Borroni, Mennini, & Samanin, 1978; Roth & Rowland, 1998; Rowland & Carlton, 1988) but differ in their pharmacological mechanism of action and other behavioral effects. For example, PHEN is an indirect dopamine agonist that increases locomotor activity. DEX (the more active stereoisomer of fenfluramine) is an indirect serotonin agonist that does not increase locomotor activity (Garattini et al., 1978).

METHOD

Subjects

Four experimentally naive, male Sprague-Dawley rats (Harlan, Indianapolis, IN), maintained at 85% ± 5% of their free-feeding weights, were used. Each rat was individually housed in a shoebox cage with free access to water. The vivarium was maintained on a 12:12 hr light/dark cycle (lights on at 6:00 a.m.) and at 70 °F. Supplemental chow was given at least 30 min after experimental sessions and on weekends to maintain stable body weights.

Apparatus

Rats were tested in four single-lever operant conditioning chambers (Grason-Stadler Model E3125B, Concord, MA), measuring 30 cm long, 20 cm high, and 29 cm wide. The response lever was located on the left side of the front wall, 8 cm above the floor. A force of approximately 0.25 N was required to operate the lever. An aperture horizontally centered on the front wall 1.5 cm above the floor allowed delivery of 45-mg food pellets (Formula A/I, P. J. Noyes, Lancaster, NH). A white stimulus light was located 7 cm above the response lever. Masking noise was provided by a white noise generator through a speaker mounted in the lower left corner of the front panel of the chamber. Each chamber was enclosed within a sound-attenuating box. A computer using MED-PC™ software (Ver. 2.0, Med Associates, St. Albans, VT) controlled experimental events and recorded data.

Procedure

Condition 1: Progressive-ratio performance. All rats were first exposed to a variable-time 60-s schedule of food delivery for magazine training. In the presence of a white stimulus light, a single food pellet was delivered on average every 60 s. Food delivery was accompanied by a 0.25 s offset of the stimulus light. Once rats reliably consumed food pellets, a fixed-ratio (FR) 1 schedule of food delivery was arranged during daily 1-hr sessions. In the presence of the white stimulus light, each lever press produced a single food pellet. Once lever pressing occurred reliably (within five sessions), the FR value was gradually increased to FR 20 over several sessions. After response rates were stable (i.e., no discernible trend

across five consecutive sessions), the schedule was changed to PR 5. Under this schedule, the ratio requirement for food delivery began at five each session and increased by five each time a food pellet was earned. A session terminated when a rat failed to press the lever for 5 consecutive minutes, completed 60 ratios (i.e., completed the terminal response requirement, which was 300 responses), or 2.5 hr elapsed, whichever occurred first. Sessions were conducted 5 days per week at about 1:00 p.m.

After breaking points stabilized under the PR schedule, saline was given before two to three sessions to acclimate animals to the injection procedure. The acute effects of DEX and PHEN were then determined. For all rats, DEX dose-response determinations were conducted first. Two determinations of each dose were obtained, each involving administration of the doses in a mixed order, including saline. All doses were administered once before any were repeated. No injections were given prior to sessions on Mondays, Wednesdays, or Thursdays. Sessions on Mondays and Thursdays served as control sessions. At least 10 sessions following the last DEX dose and when breaking points were stable (range 10 to 15 sessions), the effects of PHEN were determined. As with DEX, doses and saline were given in a mixed order. With PHEN, a third dose-response determination was conducted in 3 rats due to the variability in its effects across the first two dose-response determinations. Following assessment of PHEN, drug effects on food consumption (Condition 2) were examined.

Condition 2: Food consumption. The same rats from Condition 1 were used for Condition 2. The rats continued to be maintained at 85% of their free-feeding weights during this condition. Supplemental chow was given at least 30 min after sessions and on weekends as needed to maintain stable body weights. On Tuesday and Friday of each week, rats were placed in the same operant chamber in which they responded in Condition 1 and allowed free access to food pellets. The food pellets were identical to those delivered under the PR schedule; they were placed in a small, heavy ceramic dish on the floor. The duration of food access for a given rat was yoked to the average duration of its control sessions during Condition 1, to the nearest 10 min. Session times were 40 min, 50 min, 30 min, and 40 min for rats R1 to R4, respectively. The weight of the food dish (with pellets) was recorded before and after each session to determine the amount of food consumed. On the rare occasion when food was spilled during a session, it was collected from a pan under the chamber floor and included in the postsession weighing. Food-intake sessions were conducted at the same time of day as the PR sessions. Only two sessions were run per week, to avoid increases in body weight. All rats were initially exposed to two food-intake sessions without injections. After these sessions, the effects of saline, DEX (0.32 to 23.0 mg/kg), and then PHEN (1.0 to 30.0 mg/kg) were determined. All doses and saline were given at least twice (range two to five times) in a mixed order. Two saline sessions intervened between DEX and PHEN dose-response determinations.

Drugs

DEX (dextrofenfluramine HCl) was obtained from Wyeth-Ayerst Laboratories (Princeton, NJ). PHEN (phentermine HCl) was obtained from Sigma (St. Louis, MO). Both drugs were dissolved in saline and administered intraperitoneally (i.p.) in a volume of 1.0 ml/kg 15 min prior to sessions. All doses are expressed as the salt. Saline served as a vehicle control and was administered i.p. in a volume of 1.0 ml/kg 15 min prior to sessions.

Data Analysis

During Condition 1 (PR condition), the breaking point (defined as the number of reinforcers earned during each session), overall response rate (total responses during the session/total session duration), and response rate for each reinforcer (number of responses to earn the reinforcer/total time [seconds] to earn the reinforcer [postreinforcement pause time plus run time]) were calculated for each session. During Condition 2 (free-access condition), mean grams of food consumed per session were measured during each food consumption session. Performances during drug and control sessions were considered significantly different if the ranges of these values did not overlap. Breaking point during a drug session was calculated as a percentage of control performance. Control per-

formance was calculated as the mean breaking point across the sessions (usually Mondays and Thursdays) that immediately preceded drug-testing sessions (usually Tuesdays and Fridays). The ED_{50} values for DEX and PHEN dose-response curves were determined by fitting linear regression lines to the dose-response curves for each rat, and solving for x (dose) when the value of y (effect) was set at 50% of the vehicle control value. These ED_{50} values were then pooled to calculate a mean ED_{50} for each drug in each condition, which were compared using paired t-tests. Data are presented in the order in which drugs were tested (DEX followed by PHEN).

Results

Drug Effects Under PR Conditions

The mean breaking points during control sessions for DEX were 29.1, 36.8, 34.1, and 24.6 for rats R1 to R4, respectively. The mean response rates during these sessions were 1.2, 1.6, 1.1, and 1.2 responses per second for rats R1 to R4, respectively. Figure 1 shows the effects of DEX and PHEN on the number of reinforcers earned per session expressed as a percentage of control performance. In most cases, DEX (left column) decreased breaking points as a function of increasing dose. For 2 rats (R1 and R3), doses larger than 0.56 mg/kg decreased breaking points. For the other 2 rats, doses larger than 1.0 mg/kg decreased breaking points. In 1 rat (R4), 1.0 mg/kg increased breaking point during the first determination, but on the second determination, the breaking point was within the range of control sessions. DEX had similar effects on response rates (data not shown).

The mean breaking points during control sessions for PHEN were 30.3, 38.1, 30.1, and 19.8 for rats R1 to R4, respectively. Mean response rates during these sessions were 0.9, 1.4, 0.9, and 0.8 responses per second for rats R1 to R4, respectively. Figure 1 (right column) shows that in all rats the lowest dose of PHEN (1.0 mg/kg) produced little or no effect on breaking points across all three determinations. For 3 rats (R2, R3, R4), intermediate doses (3.2 to 5.6 mg/kg) increased breaking points during the first determination but had little or no effect during the second and third determinations. Higher doses (10.0 to 23.0 mg/kg) initially also increased breaking points in these rats. However, this effect was less prevalent across the second and third dose-response determinations, culminating in the failure of this drug to increase breaking points by the third determination (except for 10.0 mg/kg in R2). Thus there appeared to be a downward shift in the dose-effect curve across the three determinations for these 3 rats. No dose of PHEN increased breaking points in R1, but a downward shift in the breaking point dose-response curve similar to that seen in the other rats was apparent.

Visual observation of R2, R3, and R4 indicated that doses that increased breaking points during the first dose-response determination also produced repetitive, stereotyped sniffing near the response lever. Lever pressing also appeared to be part of this behavior pattern. Figure 2 shows a pattern of persistent responding that greatly extended the duration of a session for R4. This occurred during the first determination of several doses of PHEN and was associated with increases in breaking point. Similar patterns of responding were observed in the other 2 rats (R2 and R3) that exhibited increases in breaking point. With 10.0 mg/kg PHEN, local response rates at the beginning of the session were decreased, but gradually increased over the session. In addition, ratio-to-ratio variability decreased. This pattern of responding was less evident during the second and third exposures to higher doses. The persistent responding during the first exposure to higher doses in R4 resulted in a change in how sessions were typically terminated. In contrast to control sessions, these sessions terminated after completion of the highest possible ratio in the progression (FR 300). It is unknown whether higher breaking points would have been obtained in the absence of this programmed ceiling.

Drug Effects Under Free-Access Conditions

During control sessions for DEX, the mean grams of food consumed for each rat was 7.4 g, 10.2 g, 7.1 g, and 11.1 g for rats R1 to R4, respectively. Figure 3 (left column, open symbols) shows that DEX produced dose-dependent decreases in food consumption for all rats. During control sessions for PHEN, the mean amount of food consumed was 8.0 g, 11.2 g, 8.1 g, and 11.9 g for rats R1 to R4,

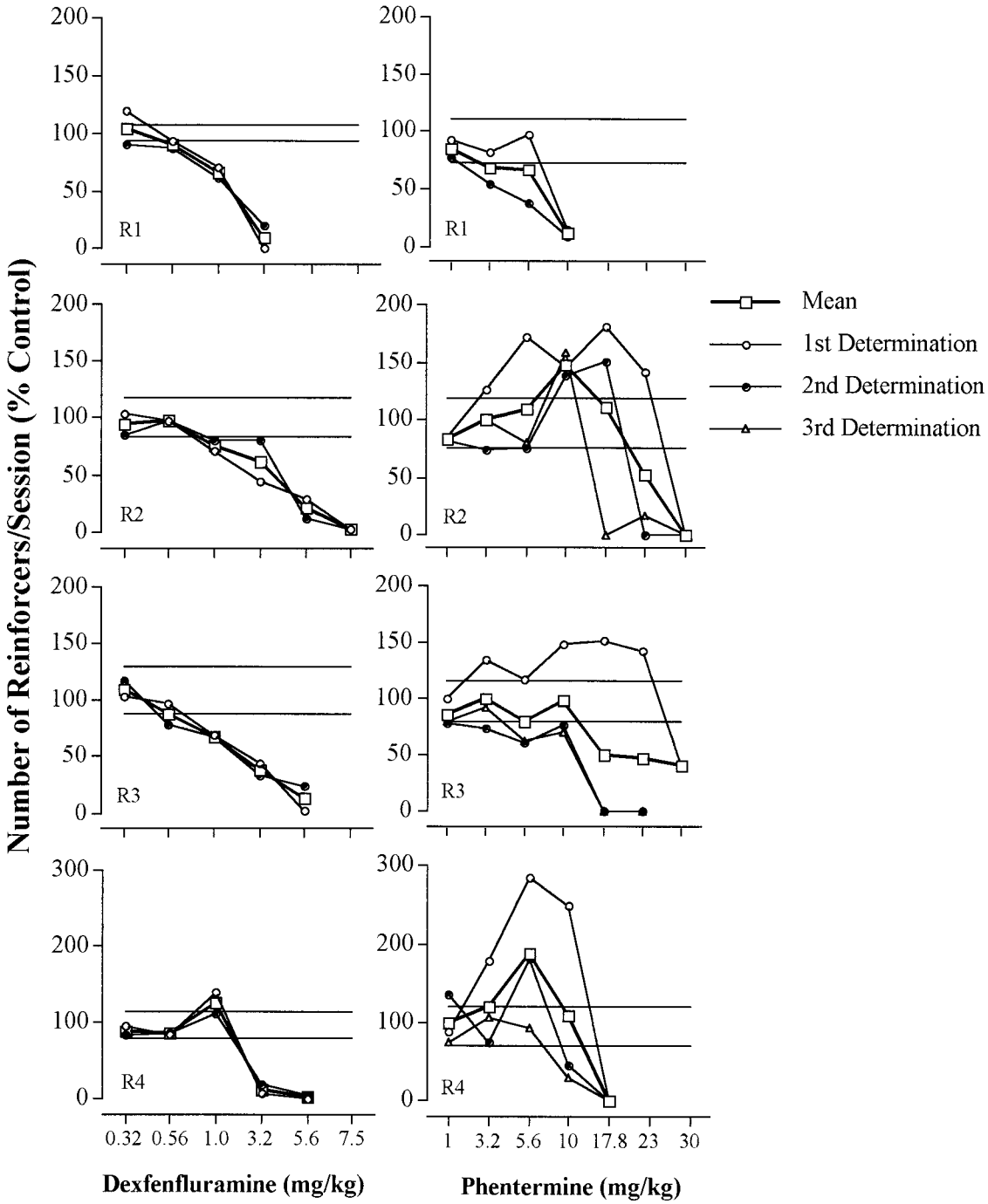

Fig. 1. Effects of DEX (left column) and PHEN (right column) on the number of reinforcers earned per session (breaking point) under a PR 5 schedule of food delivery, expressed as a percentage of control performance during sessions immediately preceding drug sessions. Solid lines with open squares represent the mean of the dose-response determinations. Horizontal lines represent the range of performance during control sessions (see text for mean control values). Each panel shows data from an individual rat. Each row of panels shows data from the same rat. Note that the *y*-axis scale is different for R4.

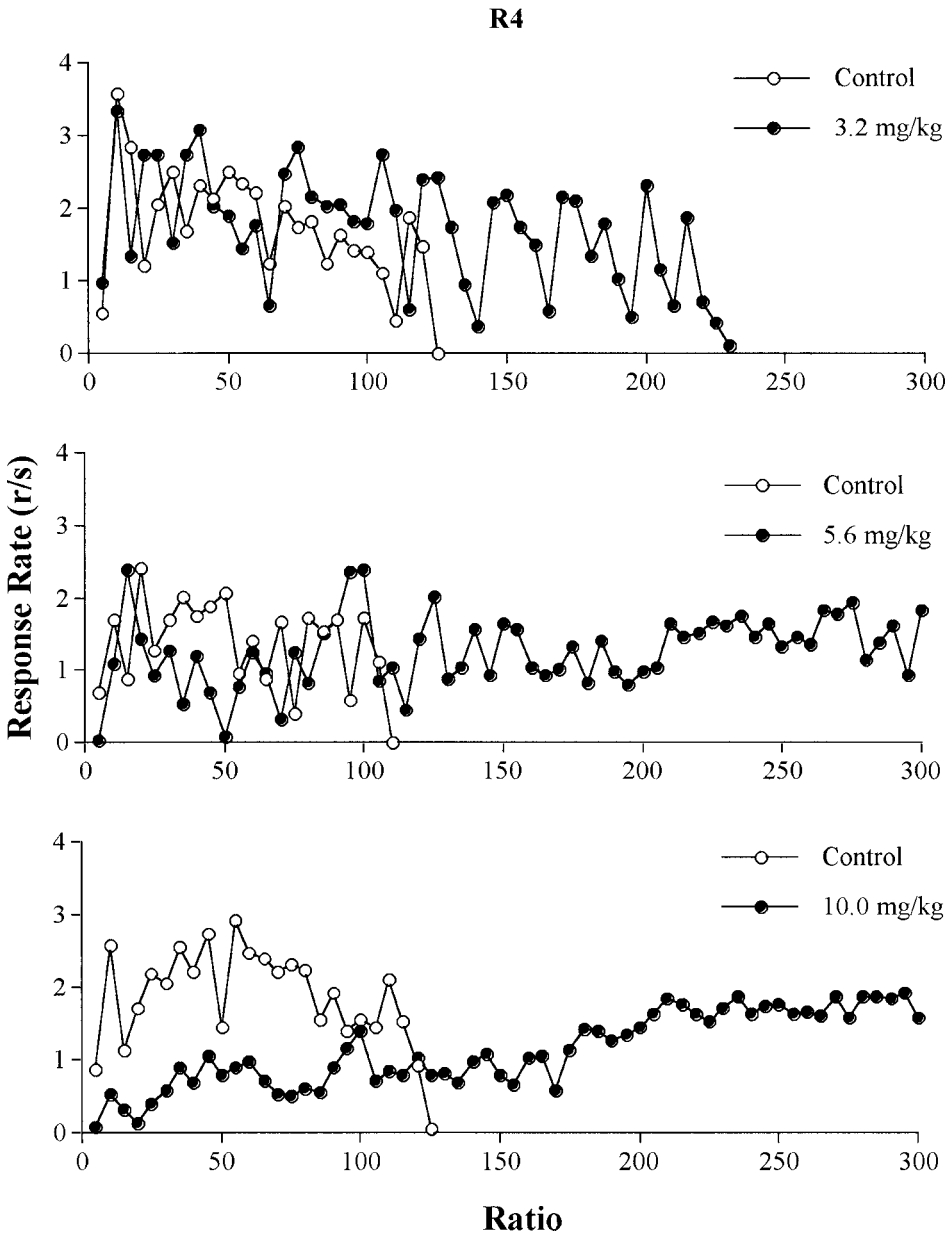

Fig. 2. Effects of PHEN on response rate (responses per second) for individual ratios under the PR 5 schedule in rat R4. Open circles represent response rates at each ratio during the control session that immediately preceded each first determination of 3.2, 5.6, or 10.0 mg/kg PHEN. Solid circles represent response rates during drug sessions.

respectively. Figure 3 (right column) shows that PHEN also decreased food consumption in all rats (only data for the first dose-response determination for PHEN was included for R4, due to illness during the second determination).

Comparisons of Drug Effects Between Conditions

To allow comparison of drug effects on breaking point and food consumption, Figure 3 shows dose-response curves for DEX

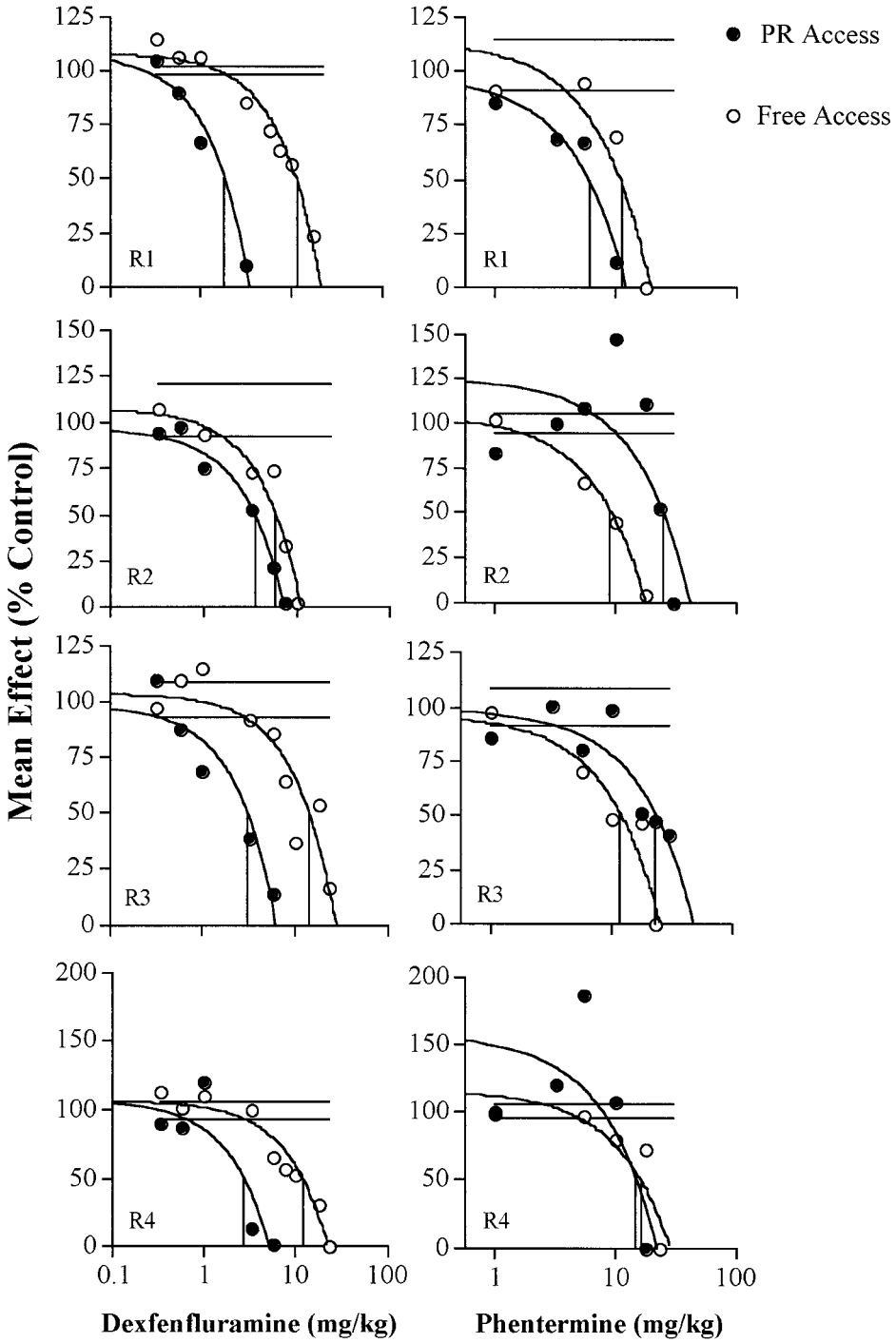

Fig. 3. Effects of DEX (left column) and PHEN (right column) on food intake (pellets consumed) under the PR schedule and free-access conditions expressed as a percentage of control intake. Open circles represent mean food intake during exposure to the indicated doses during the free-access condition. Closed circles represent the mean breaking point during exposure to the indicated doses during the PR condition (data are the same as in Figure 1). Horizontal lines represent the range of food intake during *free-access* sessions prior to which saline was administered. Vertical lines indicate ED_{50} doses for each dependent measure. Each panel shows data from an individual rat. Each row of panels shows data from the same rat. Note that the *y*-axis scale differs across rats.

Table 1

ED_{50} doses (mg/kg) of dexfenfluramine and phentermine for reducing food intake under progressive-ratio (PR) and free-access (FA) conditions. The *shift* in ED_{50} values (FA ED_{50}-PR ED_{50}) between conditions is also shown for each rat. Values greater than zero indicate that higher doses were required to decrease intake during free access, whereas values less than zero indicate that lower doses were required to decrease intake during free access. Values in the right two columns are from the third dose-response determination for PHEN only.

				Phentermine				
	Dexfenfluramine			All determinations			Third determination only	
Rat	PR ED_{50}	FA ED_{50}	Shift	PR ED_{50}	FA ED_{50}	Shift	PR ED_{50}	Shift
R1	1.84	11.39	9.55	5.98	11.03	5.05	4.17	6.86
R2	3.59	5.98	2.39	25.09	9.42	−15.70	16.13	−6.70
R3	2.99	14.07	11.10	23.72	12.20	−11.50	10.33	1.87
R4	2.75	11.86	9.11	14.96	16.43	1.47	9.37	7.06
Mean	2.79	10.83*	8.03	17.44	12.27	−5.17	10.00	2.27

* Significantly different from PR ED_{50} ($t = 4.167$, $df = 3$, $p < 0.05$).

and PHEN on both dependent measures. In general, the DEX dose-response curves for food consumption fell substantially to the right of the dose-response curves for breaking point. Table 1 shows the mean ED_{50} of both drugs for both conditions in each animal. The mean ED_{50} for DEX on food intake under the free-access condition was significantly greater (388%) than that under PR conditions. The mean ED_{50} for PHEN was not significantly different between conditions, but individual differences were apparent. The ED_{50} for food intake under the free-access condition was higher than that under the PR condition in 1 rat (R1), comparable in 1 (R4), and lower in the remaining 2 rats (R2 & R3). The ED_{50} for breaking point during only the last PHEN dose-response determination, when increases in breaking point were less frequent, was lower compared to the mean ED_{50} for all three determinations, and was not significantly different from the ED_{50} for the free-access condition.

Discussion

Both DEX and PHEN decreased food intake under the free-access condition. However, the effects of these drugs differed under the PR condition. Whereas PHEN initially produced marked increases in breaking point in some subjects, DEX did not. Previous studies have shown that moderate doses of PHEN increase locomotor activity whereas DEX only decreases locomotor activity (Garattini et al., 1978). Thus, in accordance with prior studies, the present findings suggest that anorectics with stimulant effects can increase food-maintained breaking points (Jones, LeSage, Sundby, & Poling, 1995; Poncelet, Chermat, Soubrie, & Simon, 1983; Sizemore, Cannon, Smith, & Dworkin, 2003; Thompson, 1972, 1977), whereas those without stimulant effects do not (Frederick et al., 1998; Thompson, 1977).

The present findings are consistent with those of a previous study showing that some drugs can affect food intake differently under a PR schedule and free-access conditions. Jewett el al. (1995) found that neuropeptide Y, insulin, and 2-deoxyglucose all produced similar increases in food intake under free-access conditions, but only neuropeptide Y produced significant increases in food intake under a PR schedule. The present findings indicate that the effects of some anorectic drugs on food intake also can differ across PR schedule and free-access conditions.

DEX and PHEN also differed with respect to potency in different access conditions. Whereas the ED_{50} for DEX on food intake under the free-access condition was significantly greater than that for breaking point, the ED_{50} values for PHEN were not significantly different between conditions. This finding demonstrates that the potency of DEX on food-motivated behavior depends upon the conditions of access to food, whereas the effects of PHEN are not consistently modified by access conditions. It is important to note that the ED_{50} values for the effects of DEX on free-access food intake in the present study (5.98 to 14.07 mg/kg) were significant-

ly higher than those reported in other studies of the effects of DEX on deprivation-induced food consumption (e.g., 1.25 to 2.50 mg/kg, see Rowland & Carlton, 1988). This may be due to procedural factors inherent in the design of the present study. Previous studies of the effects of DEX on food intake allowed 1- to 24-hr access to food per day for up to 2 weeks prior to drug assessment. Weight loss was typically less than 10% below nondeprived weight (e.g., Borsini, Bendotti, Aleotti, Samanin, & Garattini, 1982; Rowland & Carlton, 1988). In the present study, rats were maintained at 15% below their ad-lib weight for several months before the effects of DEX were assessed, and access periods were shorter (less than 1 hr). In addition, studies of drug effects on food intake under free-access conditions typically do not involve rats with a long history of responding under a schedule of food delivery, as was the case in the present study.

The DEX-induced reductions in breaking points under a PR 5 schedule and food intake under the free-access condition in the present study were similar to those in several reports using a variety of feeding assays (for review see Rowland & Carlton, 1988). The data also parallel those of studies showing that DEX and racemic fenfluramine decrease breaking points for food in rhesus monkeys (Frederick et al., 1998) and pigeons (Thompson, 1977). The PHEN-induced increases in breaking points observed in the present study are consistent with previous studies showing that intermediate doses of psychomotor stimulants can increase breaking points for food; for example, cocaine (Jones et al., 1995; Poncelet et al., 1983; Sizemore et al., 2003; Thompson, 1977) and amphetamine (Poncelet et al., 1983; Thompson, 1972). However, PHEN and d-amphetamine have been shown to only decrease breaking points for food in rhesus monkeys (Foltin & Evans, 2001; Negus & Mello, 2003; Schulze & Paule, 1990; Stafford, LeSage, & Glowa, 1999). It is possible that this discrepancy is due to the different species used. Consistent with other reports in both rodents (e.g., Roth & Rowland, 1998) and primates (e.g., Foltin, 1989), however, PHEN only decreased food intake under the free-access condition in the present study.

One possibility for why PHEN initially increased breaking points may be because it produced stereotypic lever pressing and a pattern of persistent responding that extended the duration of a session. Previous studies have shown that lever pressing can become part of the stereotypic pattern of responding induced by other stimulants (e.g., Collins, Lesse, & Dagan, 1979; Robbins, 1976). Unfortunately, these conclusions are speculative because stereotypy was not measured quantitatively in the present study. The downward shift in the dose-response curves suggests that tolerance may have developed to this effect, as has been seen with other stimulants (Eichler, Antelman, & Black, 1980; Nielsen, 1981; Salisbury & Wolgin, 1985). With this downward shift, the difference in effects of PHEN across the two access conditions was more similar to that seen with DEX.

In the present study, doses of PHEN that increased breaking points also produced distinctive effects on local response rates. At these doses, local response rates were decreased at the beginning of the session, followed by an increasing trend in local rates to levels comparable to those observed during control sessions. Sizemore et al. (2003) reported the same effect of cocaine under a PR schedule. To our knowledge, no other studies of psychostimulant drug effects on PR performance have reported similar data on within-session drug effects. Additional studies are needed to determine whether the within-session effects on local rates under a PR schedule observed in the present study and by Sizemore et al. are a general feature of psychostimulant drugs.

The present findings suggest that the potency of some anorectic drugs can vary as a function of the effort required to obtain food. DEX was more potent in decreasing food intake under the PR condition than under the free-access condition. Numerous studies have shown that drugs more easily disrupt responding when response requirements are more effortful; for example, larger FR size, greater response force (Hoffman, Branch, & Sizemore, 1987; Makhay, Alling, & Poling, 1994). However, PHEN did not differ in its potency across the two access conditions. Why effort would modulate the potency of DEX to a greater extent than PHEN is unclear.

EXPERIMENT 2

This experiment was designed to characterize the duration of action of DEX and PHEN on PR performance, and to see whether initial drug-induced decreases in breaking point would be followed by compensatory increases in this measure. Compensatory increases in food consumption are important from a clinical perspective because drugs that simply postpone feeding may not be very useful as anorectic medications (Foltin, 1989). This issue was addressed using a novel, five-component mixed PR schedule of food delivery, employing the same PR schedule that was used in Experiment 1 in each component. Components two through five of this extended session each began 3 hr after the beginning of the previous component.

METHOD

Subjects

Six experimentally naive, male Sprague-Dawley rats were maintained as described in Experiment 1 except they were not fed after sessions because they earned sufficient food during sessions to maintain a stable body weight.

Apparatus

Rats were tested in a different set of chambers (Med Associates, St. Albans, VT; 29 cm long, 21 cm high, and 24 cm wide) than those used in Experiment 1. Two response levers were located on the front wall 7 cm above the floor on either side of a food aperture. A force of approximately 0.14 N was required to operate the lever. The aperture was horizontally centered on the front wall 2 cm above the floor and allowed delivery of 45-mg food pellets (Formula A/I, P. J. Noyes, Lancaster, NH). A white stimulus light was located 4 cm above each response lever. A houselight located on the center of the back wall, 3 cm below the ceiling, provided ambient illumination. Masking noise was provided by a white-noise generator through a speaker mounted in the lower-left corner of the back panel of the chamber. Each chamber was enclosed within a sound-attenuating box. A computer using MED-PC® software (Ver. 2.0, Med Associates, St. Albans, VT) controlled experimental events and recorded data.

Procedure

All rats were first exposed to an FR 1 schedule of food delivery during daily 15-hr sessions that ran overnight (5:00 p.m. to 8:00 a.m.). In the presence of the white stimulus lights, a response on either lever produced a single food pellet. Food delivery was accompanied by a 0.25 s offset of the lights. Once lever pressing occurred reliably under this schedule, the FR value was gradually increased to FR 20 across several sessions. After the number of reinforcers per session stabilized under the FR 20 schedule (i.e., no discernible trend across five consecutive sessions), a PR 5 schedule similar to that used in Experiment 1 was implemented. This PR schedule progression was limited to a maximum of 80 ratios (culminating at FR 400), presses on either of the two levers counted toward the completion of the response requirement, and three food pellets were delivered for each completed ratio. After responding was stable under the PR schedule (i.e., no discernable trend in the number of reinforcers earned across five consecutive sessions), a mixed schedule consisting of five PR components was implemented. Each component terminated when a rat failed to press a lever for 5 consecutive minutes, 80 ratios were completed, or 2.5 hr elapsed, whichever occurred first. Upon termination of a component, a timeout went into effect. During timeouts, the houselight and stimulus lights were turned off and lever-presses had no programmed consequences. The second and each subsequent component of the multiple schedule began 3 hr after the start of the preceding component. Thus the minimum timeout duration was 30 min. White lights were reilluminated and the PR progression began at the beginning of the PR sequence (i.e., FR 5). Sessions were conducted 4 days per week (Monday through Thursday), at about the same time each day (5:00 p.m. to 8:00 a.m.).

After breaking points stabilized under the mixed PR schedule, the acute effects of PHEN and DEX were determined. The pharmacological procedures were identical to those described in Experiment 1. Initially, injections of saline were given prior to each Thursday session (range two to three sessions) to acclimate animals to the injection procedure. When it was clear that saline in-

jections had no effect on baseline performances, acute dose-response determinations for PHEN (1.0 to 30.0 mg/kg) and then DEX (0.56 to 3.2 mg/kg) were obtained. Each dose of each drug was given twice in a mixed order. No injections were given prior to sessions on Monday, Tuesday, or Wednesday (sessions were not run on Fridays). At least 10 sessions (range 10 to 28 sessions) and confirmation of a stable baseline separated PHEN and DEX dose-response determinations.

Data Analysis

During each session, the total reinforcers earned for the entire session, breaking point (number of reinforcers) in each component, overall response rate across all five components (total responses in all components/total duration [minutes] of all components), response rate in each component (total responses in a component/minutes in a component), and response rate for each reinforcer (number of responses to earn the reinforcer/total time [seconds] to earn the reinforcer [postreinforcement pause time plus run time]) in each component were measured. Performances during drug and control sessions were considered significantly different if the ranges of these values did not overlap. Breaking point during each component of a drug session was calculated as a percentage of control performance, which was calculated as the mean breaking point during the same component across all sessions that were immediately preceded by saline injections. Data are presented in the order in which drugs were tested (PHEN followed by DEX).

Results

Figure 4 shows the effects of PHEN and DEX on the total number of reinforcers earned for a session as a function of dose. During control sessions, the number of reinforcers earned varied among rats. For 4 rats, the total number of reinforcers earned was relatively high, from about 110 to 160. For 2 other rats (R7 and R9) the total number of reinforcers earned was relatively low, from about 45 to 60. Session averages were stable. PHEN decreased total reinforcers as an increasing function of dose in 4 rats (R5, R6, R8, and R10). For R5, only the largest dose significantly decreased total reinforcers. In contrast, PHEN increased total reinforcers earned in the 2 rats (R7 and R9) with low baseline-session breaking points, and higher doses failed to decrease this measure. DEX decreased total reinforcers as a function of increasing dose in 5 of 6 rats, but had little effect on this measure in R9. This figure also shows that DEX was more potent than PHEN in decreasing the total reinforcers earned per session.

Figure 5 shows the effects of PHEN on the mean number of reinforcers earned in each component of the mixed PR 5 schedule. During control sessions (shaded areas) breaking points decreased across components in the 4 rats (R5, R6, R8, and R10) with relatively high breaking points (more than 30 reinforcers) in the first component. In contrast, breaking points remained stable over control sessions in the 2 rats (R7 and R9) with relatively low breaking points (less than or equal to 15 reinforcers) in the first component. PHEN produced a dose-dependent decrease in the number of reinforcers obtained in the first component in 4 of 6 rats (R5, R6, R8, and R10). In the other 2 rats, intermediate doses of PHEN (5.6 mg/kg for R7, and from 5.6 to 23.0 mg/kg for R9) increased reinforcers obtained in the first component whereas larger doses decreased that measure. When PHEN decreased the number of reinforcers obtained in the first component, breaking points often increased relative to mean control breaking points across subsequent components. Occasionally, these increases in breaking point exceeded the control range. For example, 17.8 mg/kg PHEN decreased breaking points in the first component for R7. During the second component, however, breaking points markedly increased compared to control. Consequently, there was no significant effect on the total number of reinforcers earned per session at this dose (see Figure 4).

Figure 6 shows the effects of DEX on the mean number of reinforcers earned in each component of the mixed PR schedule. Control performance was similar to that observed during PHEN dose-response determinations. DEX produced a dose-dependent decrease in breaking point in the first component in all rats. Following significant drug-induced reductions in breaking point in the

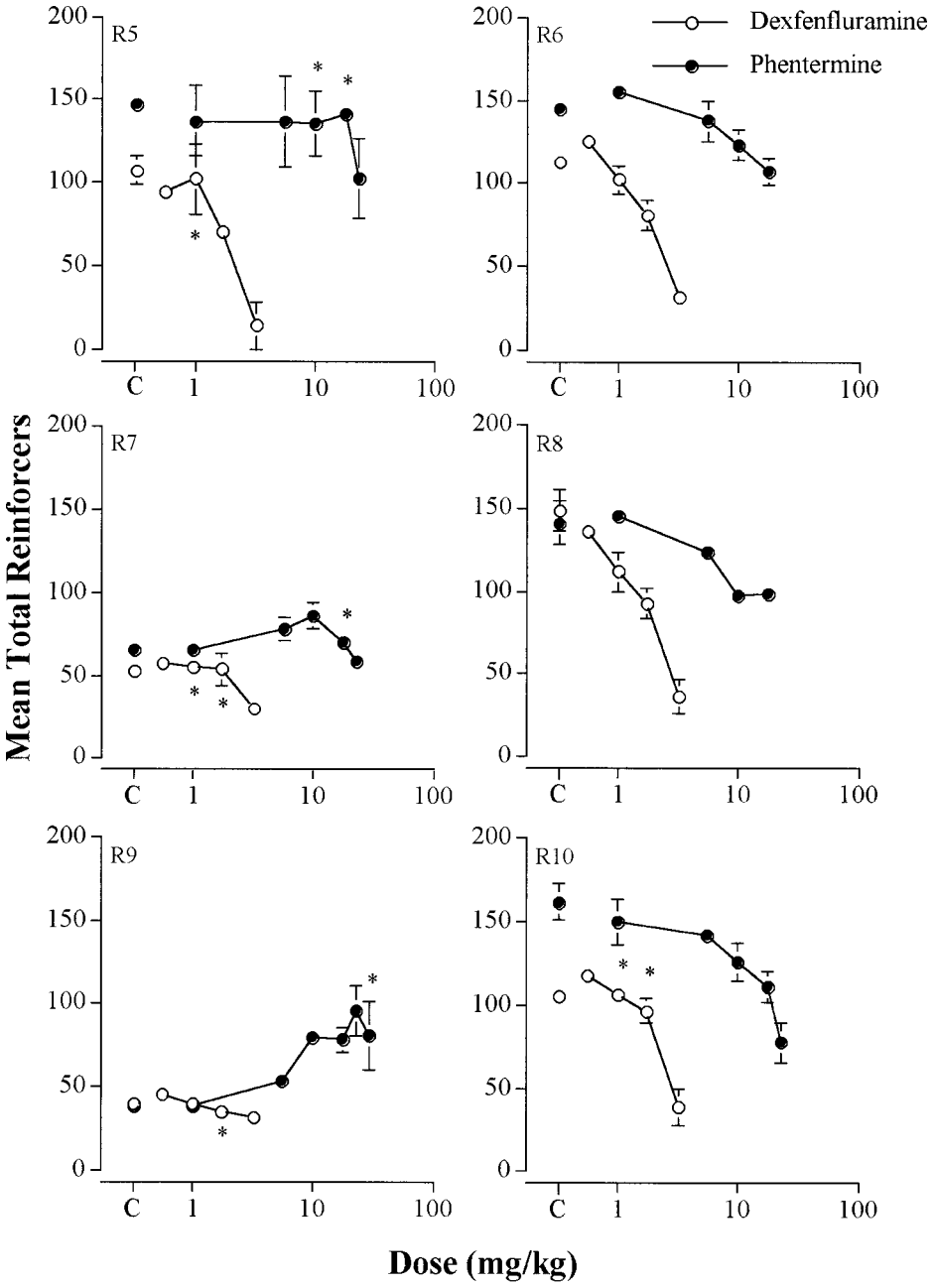

Fig. 4. Effects of DEX and PHEN on the mean total reinforcers earned under the mixed PR schedule of food delivery. Each panel shows data for an individual rat. Each data point represents the mean number of reinforcers earned across two administrations of the indicated dose of drug. Vertical lines represent the range. Points without vertical lines are instances in which the range is encompassed by the point. Points above C represent performance following administration of saline. Solid circles represent data for PHEN dose-response determinations and open circles represent data for DEX dose-response determinations. Asterisks indicate doses that significantly reduced the number of reinforcers earned in the first component (see Figures 5 and 6) but had no significant effect on total reinforcers earned for the session.

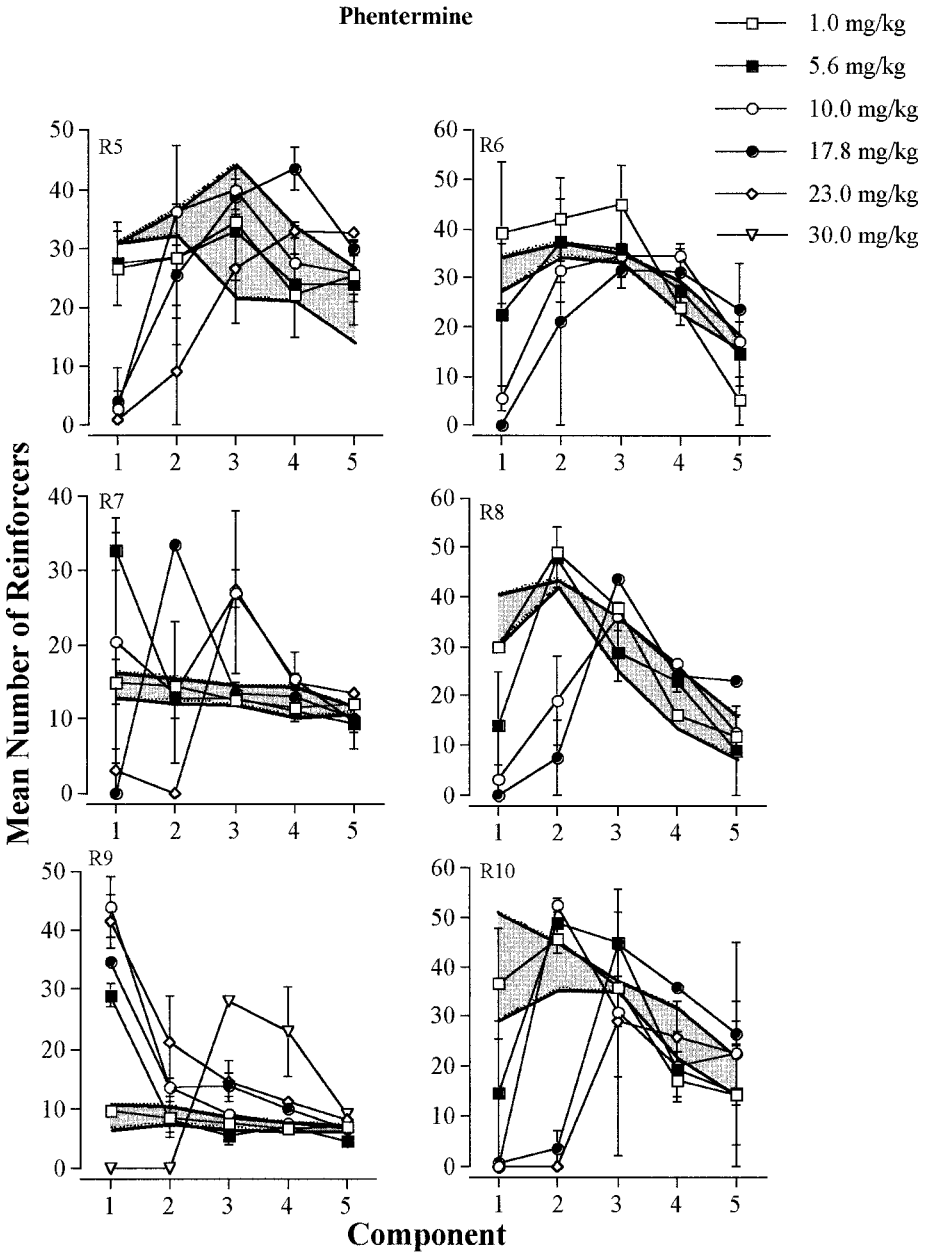

Fig. 5. Effects of PHEN on the mean number of reinforcers earned in each component under the multiple PR schedule of food delivery. Each panel shows data for an individual rat. Each data point represents the mean number of reinforcers earned across two administrations of the indicated dose of drug. Vertical lines represent the range. Points without vertical lines are instances in which the range is encompassed by the point. Shaded areas represent the range following administrations of saline.

first component, breaking points across subsequent components increased relative to the first component. For example, low doses of DEX decreased breaking points in the first component for R6, R7, and R10, and increased them in later components. However, the total number of reinforcers per session did not increase. For 3 rats (R5, R8,

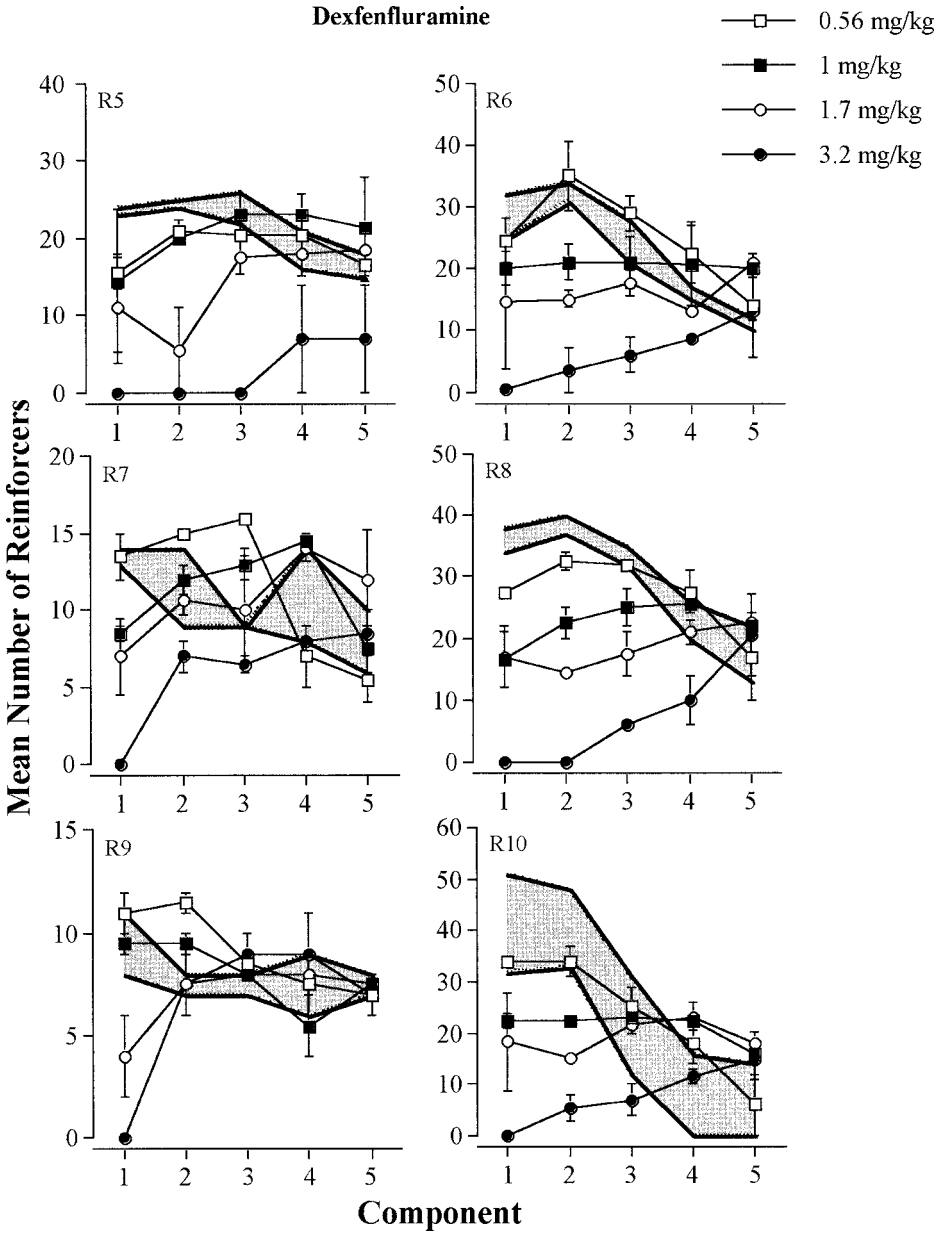

Fig. 6. Effects of DEX on the mean number of reinforcers earned in each component under the multiple PR schedule of food delivery. See Figure 5 caption for more details.

R9), breaking points only returned to control levels in later components after significant decreases in breaking points in the first component.

To facilitate comparison of the time course of drug effects on breaking point, Figure 7 shows the mean breaking point in each component, as a percentage of saline control, for the different doses of each drug. The time to recover baseline performance increased as a function of dose for both drugs. In the range of doses tested, the duration of the effect of PHEN on breaking point was shorter than that for DEX.

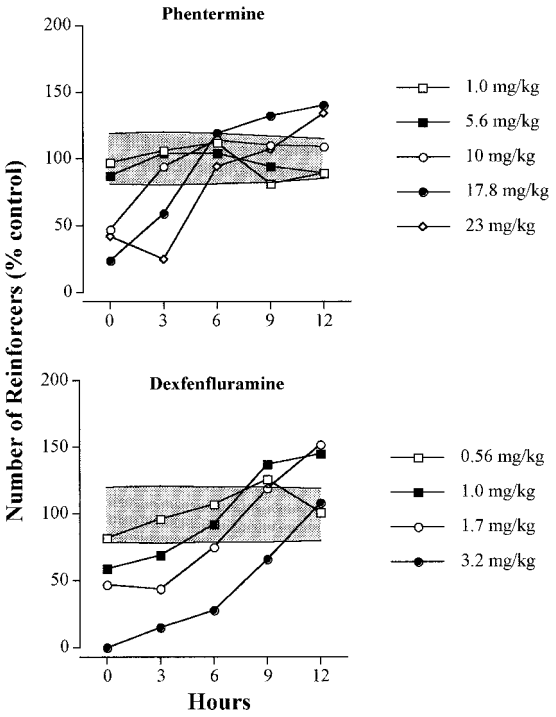

Fig. 7. Effects of PHEN and DEX on the number of reinforcers earned in each component (as a percentage of saline control) under the mixed PR schedule of food delivery. Data are plotted as a function of hour from the beginning of the first component. Each point represents the mean data from 6 rats. See Figure 5 caption for more details.

Discussion

Both DEX and PHEN produced dose-dependent decreases in the number of reinforcers earned in the first component of the mixed PR schedule in most rats. This finding is generally consistent with the results of Experiment 1 and prior studies showing that DEX and PHEN reduce food consumption in a variety of species and feeding assays (e.g., Foltin, 1989; Garattini et al., 1978; Roth & Rowland, 1998; Rowland & Carlton, 1988). DEX was also more potent than PHEN in reducing the number of reinforcers earned under the PR schedule, consistent with the findings of Experiment 1 and prior studies (Maickel & Johnson, 1973; Roth & Rowland, 1998; Shoaib, Baumann, Rothman, Goldberg, & Schindler, 1997). PHEN-induced increases in the number of reinforcers earned were observed in 3 of 4 rats in Experiment 1, but this effect was obtained in only 2 of 6 rats in Experiment 2 (R7, R9). In Experiment 2, the chamber was slightly larger than that used in Experiment 1, two levers were present, responses on both levers counted toward completion of the ratio, three pellets were delivered following completion of each ratio, the order of drug testing was reversed, and multiple components were employed. In addition, drug testing occurred at a different time of the day, and recovery of performance within the session occurred. Any one or a combination of these variables may have accounted for the lower incidence of PHEN-induced increases in breaking point in Experiment 2.

When doses of PHEN were sufficiently high to decrease breaking points in the first component, breaking point in later components of the session was occasionally increased above control levels, but this did not affect the total number of reinforcers per session (noted by asterisks in Figure 4). This finding is consistent with prior reports showing that compensatory increases in food consumption can occur following initial decreases produced by PHEN and other psychomotor stimulants (Caul, Jones, & Barrett, 1988; Foltin, 1989; Foltin, Fischman, & Nautiyal, 1990; Jones & Caul, 1989). In contrast, high doses of PHEN decreased food consumption in baboons for up to 22 hr (Foltin, 1989). These baboons were not food deprived, which may account for the longer time course of drug effects for PHEN.

Following doses of DEX that decreased breaking points in the first component, increases above control breaking point in later components of the session were less frequent than with PHEN. In 4 of 6 rats (R5, R7, R9, R10), compensatory increases in the number of reinforcers earned in later components resulted in no change in mean total reinforcers earned for the entire session following exposure to 1.0 or 1.7 mg/kg DEX (see Figure 4). This finding is consistent with prior reports showing that compensatory increases in food consumption can occur following fenfluramine treatment (e.g., Burton, Cooper, & Popplewell, 1981; Roth & Rowland, 1998). However, another study showed that although compensatory increases in food consumption were observed in rats following fenfluramine-induced decreases, total intake for an entire 23-hr session remained suppressed (Burton et al., 1981). These studies were accomplished with the racemic mixture of fenflur-

amine, as opposed to DEX, and the rats in the Burton et al. study were not food deprived. These factors may account for the discrepancy with the present study.

GENERAL DISCUSSION

Several findings emerge from the present experiments. First, both DEX and PHEN reduced food intake under free-access conditions in a dose-dependent fashion. Second, although high doses of both DEX and PHEN decreased breaking points under a PR schedule of food delivery, PHEN increased breaking points at moderate doses whereas DEX did not. Third, DEX was more potent in decreasing breaking points under the PR schedule than decreasing food intake under the free-access condition, whereas PHEN did not consistently differ in potency across access conditions. Fourth, the duration of action of DEX under the five-component mixed PR schedule was longer than that for PHEN. Fifth, after doses of either drug decreased breaking points early in the session, breaking points in later components of sessions exceeded control levels, resulting in no significant effect on the total numbers of reinforcers obtained per session in some rats (i.e., compensatory food intake was observed). Overall, the differences in effects between the two drugs provide some interesting perspectives on their anorectic properties.

Both DEX and PHEN decreased food consumption when food was freely available, consistent with previous studies (Roth & Rowland, 1998; Rowland & Carlton, 1988). However, DEX (but not PHEN) was more potent when PR responding was required than when food was freely available. The failure to find differences in potency for PHEN between the two access conditions appears to be due to PHEN often increasing breaking points. For instance, during the third dose-response determination in Experiment 1 (see Table 1), when increases in breaking point were less apparent, PHEN was more potent in reducing food intake under the PR schedule in most rats. The greater potency of the drugs in reducing food intake under the PR schedule is consistent with numerous studies indicating that increased response requirements decrease the dose required to disrupt behavior (Foltin, 1997; Hoffman et al., 1987; LeSage, Stafford, & Glowa, 1999; Seiden & Campbell, 1974; Stafford, Rice, Lewis, & Glowa, 2000), although response requirement does not always modulate drug effects (e.g., Foltin & Evans, 2001).

Most studies of drug effects on PR performance have found that stimulant-type anorectic drugs increase breaking points maintained by food (Frederick et al., 1998; Jones et al., 1995; Poncelet et al., 1983; Sizemore et al., 2003; Thompson, 1977; but see Caul & Brindle, 2001 and Gylys, 1967) and that anorectic drugs without stimulant effects do not (Frederick et al., 1998; Gylys, 1967; Thompson, 1977). The reason for such increases in breaking points remains unclear. The failure to consistently find increased breaking points with PHEN across both experiments suggests that psychomotor stimulant-induced increases in breaking points maintained by food is a capricious phenomenon. Since anorectic drugs without stimulant effects have not been found to increase breaking points, this phenomenon may be related to some unique effect of psychomotor stimulant drugs, such as their ability to induce stereotypy. Further studies that examine the potential role of stereotypy in the within-session effects of stimulant drugs on local response rates under PR schedules may help elucidate the behavioral mechanisms underlying stimulant-induced increases in PR breaking points.

Given that breaking points under PR schedules are considered to provide an index of the reinforcing or motivational strength of the scheduled event (e.g., food delivery: Hodos, 1961; Hodos & Kalman, 1963), the present data could indicate that both DEX and PHEN decrease the reinforcing effectiveness of food. In contrast, PHEN occasionally increased breaking points, an unexpected effect for an anorectic drug. PHEN's ability to increase locomotor and stereotypic behavior may have affected operant responding. If so, this would suggest that drug-induced increases in breaking point can occur through behavioral mechanisms other than those related to the reinforcing effects of food. Previous studies have concluded that drug-induced changes in breaking point do not provide an uncontaminated index of the reinforcing effectiveness of the scheduled reinforcer (Jones et al., 1995; Poling, LeSage, Roe, & Schaefer, 1996). In a similar vein, decreases

in breaking points also should be interpreted with caution.

To our knowledge, the present study is the first to employ a mixed PR schedule of food delivery to examine the time course of drug effects on food-maintained behavior. In Experiment 2, the time course of DEX was longer than that for PHEN. This finding is consistent with prior pharmacokinetic studies in rats that report a longer plasma half-life for DEX (156 min; Caccia, Ballabio, Guiso, Rocchetti, & Garattini, 1982; Jori, De Ponte, & Caccia, 1978) than for PHEN (86 min; Cho, Hodshon, Lindeke, & Miwa, 1973). However, if larger doses of PHEN had been given this difference might have been reduced. In addition, the ability to detect compensatory increases in performance under the multiple PR schedule suggests that the procedure also may be useful to assess ''rebound phenomena.'' These phenomena may have important clinical implications, such as counter-therapeutic increases in food-seeking behavior (Lupolover & Ward, 1982). Whether such effects would abate with chronic administration (repeated DEX has been reported to produce contingent tolerance, Roth & Rowland, 1998), may be of some interest.

The present study showed that the effects of two anorectic drugs on behavior maintained by food could differ, depending upon both the drug and access conditions. The nonstimulant anorectic (DEX) decreased food-associated performances to a greater extent when more effort was required. The stimulant anorectic (PHEN) did not decrease food-associated performances to a greater extent when more effort was required, but this lack of difference may have been contaminated by other psychomotor stimulant effects. Recovery of food-maintained responding differed for each drug, and compensatory increases were observed following moderate to high doses of both. Further studies should assess the effects of repeated exposure to anorectics, which is how humans typically use them.

REFERENCES

Bays, H., & Dujovne, C. (2002). Pharmacotherapy of obesity: Currently marketed and upcoming agents. *American Journal of Cardiovascular Drugs, 2,* 245–253.

Borsini, F., Bendotti, C., Aleotti, A., Samanin, R., & Garattini, S. (1982). D-Fenfluramine and D-norfenfluramine reduce food intake by acting on different serotonin mechanisms in the rat brain. *Pharmacological Research Communications, 14,* 671–678.

Burton, M. J., Cooper, S. J., & Popplewell, D. A. (1981). The effect of fenfluramine on the microstructure of feeding and drinking in the rat. *British Journal of Pharmacology, 72,* 621–633.

Caccia, S., Ballabio, M., Guiso, G., Rocchetti, M., & Garattini, S. (1982). Species differences in the kinetics and metabolism of fenfluramine isomers. *Archives Internationales de Pharmacodynamie et de Therapie, 258,* 15–28.

Caul, W. F., & Brindle, N. A. (2001). Schedule-dependent effects of haloperidol and amphetamine: Multiple-schedule task shows within-subject effects. *Pharmacology Biochemistry and Behavior, 68,* 53–63.

Caul, W. F., Jones, J. R., & Barrett, R. J. (1988). Amphetamine's effects on food consumption and body weight: The role of adaptive processes. *Behavioral Neuroscience, 102,* 441–450.

Cho, A. K., Hodshon, B. J., Lindeke, B., & Miwa, G. T. (1973). Application of quantitative GC-mass spectrometry to study of pharmacokinetics of amphetamine and phentermine. *Journal of Pharmaceutical Sciences, 62,* 1491–1494.

Collins, J. P., Lesse, H., & Dagan, L. A. (1979). Behavioral antecedents of cocaine-induced sereotypy. *Pharmacology Biochemistry and Behavior, 11,* 683–687.

Eichler, A. J., Antelman, S. M., & Black, C. A. (1980). Amphetamine stereotypy is not a homogenous phenomenon: Sniffing and licking show distinct profiles of sensitization and tolerance. *Psychopharmacology, 68,* 287–20.

Foltin, R. W. (1989). Effects of anorectic drugs on the topography of feeding behavior in baboons. *Journal of Pharmacology and Experimental Therapeutics, 249,* 101–109.

Foltin, R. W. (1997). Food and amphetamine self-administration by baboons: Effects of alternatives. *Journal of the Experimental Analysis of Behavior, 68,* 47–66.

Foltin, R. W., Fischman, M. W., & Nautiyal, C. (1990). The effects of cocaine on food intake of baboons before, during, and after a period of repeated desipramine. *Pharmacology Biochemistry and Behavior, 36,* 869–874.

Foltin, R. W., & Evans, S. M. (2001). The effects of D-amphetamine on responding for candy and fruit drink using a fixed ratio and a progressive ratio schedule of reinforcer delivery. *Pharmacology Biochemistry and Behavior, 69,* 125–131.

Frederick, D., Ali, S. F., Gillam, M. P., Gossett, J., Slikker, W., & Paule, M. G. (1998). Acute effects of dexfenfluramine (d-FEN) and methylenedioxymethamphetamine (MDMA) before and after short-course, high-dose treatment. *Annals of the New York Academy of Sciences, 844,* 183–190.

Garattini, S., Borroni, E., Mennini, T., & Samanin, R. (1978). Differences and similarities among aorectic agents. In S. Garrattini & R. Samanin (Eds.), *Central mechanisms of anorectic drugs* (pp. 127–143). New York: Raven Press.

Gibbs, J., & Smith G. P. (1982). Gut peptides and food in the gut produce similar satiety effects. *Peptides, 3,* 553–557.

Gylys, J. A. (1967). Anorectic agents and progressive ratio

in the rat. *Archives Internationales de Pharmacodynamie et de Therapie, 169,* 354–361.

Halford, J. C. G., Wanninayake, S. C. D., & Blundell, J. E. (1998). Behavioral satiety sequence (BSS) for the diagnosis of drug action on food intake. *Pharmacology Biochemistry and Behavior, 61,* 159–168.

Hodos, W. (1961). Progressive ratio as a measure of reward strength. *Science, 6,* 387–392.

Hodos, W., & Kalman, G. (1963). Effects of increment size and reinforcer volume on progressive ratio performance. *Journal of the Experimental Analysis of Behavior, 6,* 387–392.

Hoffman, S. H., Branch, M. N., & Sizemore, G. M. (1987). Cocaine tolerance: Acute vs. chronic effects as dependent upon fixed-ratio size. *Journal of the Experimental Analysis of Behavior, 47,* 363–376.

Jewett, D. C., Cleary, J., Levine, A. S., Schaal, D. W., & Thompson, T. (1995). Effects of neuropeptide Y, insulin, 2-deoxyglucose, and food deprivation on food-motivated behavior. *Psychopharmacology, 120,* 267–271.

Jones, C. A., LeSage, M., Sundby, S., & Poling, A. (1995). Effects of cocaine in pigeons responding under a progressive-ratio schedule of food delivery. *Pharmacology Biochemistry and Behavior, 50,* 527–531.

Jones, J. R., & Caul, W. F. (1989). Time course of the effect of amphetamine on eating is biphasic. *Behavioral Neuroscience, 103,* 1047–1052.

Jori, A., De Ponte, P., & Caccia, S. (1978). Stereoselective disposition of fenfluramine enantiomers in the rat. *Xenobiotica, 8,* 583–588.

Kennedy, J. M., & Baldwin, B. A. (1972). Taste preferences in pigs for nutritive and non-nutritive sweet solutions. *Animal Behavior, 20,* 706–718.

LeSage, M., Stafford, D., & Glowa, J. R. (1999). Preclinical research on cocaine self-administration: Environmental determinants and their interactions with pharmacological treatment. *Neuroscience and Biobehavioral Reviews, 23,* 717–741.

Lupolover, R., & Ward, D. J. (1982). Rebound phenomena: Results of a 10 years' (1970–1980) literature review. *International Pharmacopsychiatry, 17,* 194–237.

Maickel, R. P., & Johnson, S. A. (1973). Effects of various anorexigenic agents on open field behavior of rats. *Research and Communications in Chemical and Pathological Pharmacology, 6,* 733–739.

Makhay, M., Alling, K., & Poling, A. (1994). Effects of cocaine on fixed-ratio responding of rats: Modulation by required response force. *Pharmacology Biochemistry and Behavior, 48,* 511–514.

Negus, S. S., & Mello, N. K. (2003). Effects of chronic d-amphetamine treatment on cocaine and food-maintained responding under a progressive-ratio schedule in rhesus monkeys. *Psychopharmacology, 167,* 324–332.

Nielsen, E. B. (1981). Rapid decline of stereotyped behavior in rats during constant one-week administration of amphetamine via implanted ALZET osmotic minipumps. *Pharmacology Biochemistry and Behavior, 15,* 161–165.

Poling, A., LeSage, M., Roe, D., & Schaefer, D. (1996). Acute and chronic effects of morphine in pigeons responding under a progressive-ratio schedule of food delivery. *Pharmacology Biochemistry and Behavior, 54,* 485–490.

Poncelet, M., Chermat, R., Soubrie, P., & Simon, P. (1983). The progressive-ratio schedule as a model for studying the psychomotor stimulant activity of drugs in the rat. *Psychopharmacology, 80,* 184–189.

Robbins, T. W. (1976). Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. *Nature, 264,* 57–59.

Roth, J. D., & Rowland, N. E. (1998). Efficacy of administration of dexfenfluramine and phentermine, alone and in combination, on ingestive behavior and body weight in rats. *Psychopharmacology, 137,* 99–106.

Rowland, N. E., & Carlton, J. (1988). Dexfenfluramine: Effects on food intake in various animal models. *Clinical Neuropharmacology, 11,* S33-S50.

Salisbury, J. J., & Wolgin, D. L. (1985). Role of anorexia and behavioral activation in amphetamine-induced suppression of feeding: Implications for understanding tolerance. *Behavioral Neuroscience, 99,* 1153–1161.

Schulze, G. E., & Paule, M. G. (1990). Acute effects of d-amphetamine in a monkey operant behavioral test battery. *Pharmacology Biochemistry and Behavior, 35,* 759–765.

Seiden, L. S., & Campbell, A. B. (1974). Catecholamine, drugs, and behavior: Mutual interactions. In E. Usdin (Ed.), *Neuropsychopharmacology of monoamines and their regulatory enzymes* (pp. 325–338). New York: Raven Press.

Shoaib, M., Baumann, M. H., Rothman, R. B., Goldberg, S. R., & Schindler, C. W. (1997). Behavioural and neurochemical characteristics of phentermine and fenfluramine given separately and as a mixture in rats. *Psychopharmacology, 131,* 296–306.

Sizemore, G. M., Cannon, D. G., Smith, J. E., & Dworkin, S. I. (2003). The effects of acutely administered cocaine on responding maintained by a progressive-ratio schedule of food presentation. *Behavioural Pharmacology,* 14, 33–40.

Spanswick D., & Lee K. (2003). Emerging antiobesity drugs. *Expert Opinion on Emerging Drugs, 8,* 217–237.

Stafford, D., LeSage, M. G., & Glowa, J. R. (1999). Effects of phentermine on responding maintained by progressive-ratio schedules of cocaine and food delivery in rhesus monkeys. *Behavioural Pharmacology, 10,* 775–784.

Stafford, D., Rice, K. C., Lewis, D. B., & Glowa, J. R. (2000). Response requirements and unit dose modify the effects of GBR 12909 on cocaine-maintained behavior. *Experimental and Clinical Psychopharmacology, 8,* 539–548.

Thompson, D. M. (1972). Effects of d-amphetamine on the breaking point of progressive-ratio performance. *Psychonomic Science, 29,* 282–284.

Thompson, D. M. (1977). Effects of cocaine and fenfluramine on progressive-ratio performance. *Pharmacology Biochemistry and Behavior, 7,* 555–558.

Received October 2, 2000
Final acceptance August 9, 2004